REMARKS

Applicants respectfully note and reiterate that the correspondence address for the attorneys of record for this application is Fish & Neave, 1251 Avenue of the Americas, New York, NY 10020. In their replies of August 29,2002 and March 19, 2003, applicants provided the documents to support their request. Accordingly, applicants request that the Examiner make note of the correct correspondence address.

THE REJECTION

35 U.S.C. § 103(a): Claims 1-3, 5 and 6

The Examiner has maintained the rejection of claims 1-3, 5 and 6 under 35 U.S.C.§ 103(a). The Examiner contends that these claims are unpatentable over Keck et al., U.S. patent 6,040,431 ("Keck") in view of Griffith et al., Proc. Natl. Acad. Sci, 93, pp. 878-883 (1996) ("Griffith"), Luyten et al., WO96/14335 ("Luyten"), Qian et al., Proc. Natl. Acad. Sci, 89, pp. 6290-6294 (1992) ("Qian") and Daopin et al., Science, 257, pp. 369-373 (1992) ("Daopin"). The Examiner states that Keck and Qian swap domains between different TGF-β superfamily members and retain the biological activity. The Examiner also contends that the teachings of these documents in combination provide the motivation to one

of skill in the art at the time of filing to modify the TGF-β superfamily because the sequences for the finger and heel regions may be swapped from the respective finger and heel region sequences of any known member of the TGF-β superfamily. The Examiner further states that Qian provides a reasonable expectation of success and a motivation to select CDMP-2 domains for the chimera because CDMP-2 has chondrogenic activity in vivo but substantially no osteogenic activity. The Examiner contends that the use of chimeric molecules would be a practical approach to investigating the structure/function relationships of OP-1 and CDMP-2, and the only stable form in solution of such a chimeric molecule would reasonably be expected to be a dimer. The Examiner states that Daopin teaches the close structural similarity between TGF-β2 and BMP-2 and suggests that the only stable form of TGF-β2 is a dimer. Therefore, the Examiner concludes that it would have been obvious to the skilled worker at the time of the invention to make a dimer because of the close structural similarity between TGF-β2 and BMP-2 and the only stable form of TGF-β2 is a dimer. Applicants traverse.

Applicants respectfully submit that the claims are non-obvious over Keck, in combination with Luyten, Griffith,

Qian and Daopin. Rejected claims 1-3, 5 and 6 are directed to a chimeric molecule, i.e., they are composition of matter claims. Yet, the Examiner's statement that the use of chimeric molecules would be a practical approach to investigating the structure/function relationships of OP-1 and CDMP-2 amounts to no more than a statement that it is "obvious to try". It looks to whether or not it would be obvious to make the chimeric molecule. That is not the law. The proper standard is whether or not the claimed chimeric molecules would have been obvious.

The Federal Circuit's position on obviousness is clear: a composition of matter is not rendered obvious even if the method of making the composition of matter may be obvious or obvious to try. The Court has repeatedly expressly rejected arguments such as the one made by the Examiner that an obvious method renders the composition obvious. As described below, there is no teaching or suggestion by the combination of Keck, Luyten, Griffith, Qian and Daopin of a dimeric chimeric TGF-β superfamily protein wherein one monomer comprises a CDMP-2 finger 2 subdomain and a finger 1 and heel subdomain from a second member of the superfamily. Applicants respectfully submit that at the time of the invention, the claimed chimeric molecules of the TGF-β

superfamily would not have been obvious to the skilled worker.

Keck merely discloses the amino acid residues that make up finger 1, heel and finger 2 subdomains of the various members of TGF-β superfamily wherein the finger 1, heel and finger 2 subdomains are from the same member of the superfamily (see Keck, column 11, lines 59-64). Keck discloses single chain polypeptides of the TGF-β superfamily comprising a finger 1, heel and finger 2 domain joined by linker sequences that differ from the naturally occurring TGF-β superfamily members, which are inactive as monomers, in that they are functional monomer subunits. Keck also discloses that the linker sequences which join the finger 1, heel and finger 2 subdomains maintain them in their proper conformation and maintain their relative positions and orientations in space (see Keck, e.g., column 4, lines 52-58). Therefore, the skilled worker reading Keck would believe that the linker sequences are important to the maintain proper conformation and orientation and thus, proper biological activity.

Moreover, contrary to the Examiner's assertion, Keck does not teach or suggest that the finger 1, heel and

finger 2 subdomains of different members of the TGF-β superfamily may be swapped. Rather, Keck dicloses that the three subdomains are from the same member of the superfamily. And, none of Qian, Luyten, Griffith or Doapin remedy the deficiency in Keck.

Qian discloses a TGF-β chimera of two TGF-β isoforms (TGF-β1 and TGF-β2) comprising amino acid residues 1-39 of TGF-β2 linked to amino acid residues 40-82 of TGF-β1 linked to amino acid residues 83-122 of TGF-β2. Qian does not provide the motivation to make a chimeric molecule as claimed in the instant application. First, Qian's chimeric molecules are of TGF-β isoforms that share greater than 70% identity. the three regions (residues 1-39, 40-82 and 83-122) described in Qian do not correspond to the finger 1, heel and finger 2 domains recited in the claims of the instant application. Amino acid residues 1-39 of Qian span finger 1 and a portion of the heel subdomains of the proteins of the present invention, residues 40-82 span a portion of the heel and a portion of the finger 2 domains as defined in the instant application and residues 83-122 span a portion of the finger 2 subdomain and contains additional sequence on the C-terminal end of the protein. Second, Qian discloses a

chimeric molecule wherein the finger 1 and portion of the heel domain and a portion of the finger 2 domain are from the same member (TGF-β2) whereas a portion of the heel and finger 2 domains are from a different member (TGF-β1) of the superfamily. The claims of the present application, however, recite a protein wherein finger 2 is from CDMP-2 and finger 1 and heel domains are from another member of the superfamily.

Moreover, contrary to the Examiner's assertion, Qian does not provide a reasonable expectation of success and a motivation to select CDMP-2 domains for the chimera. In fact, Qian teaches just the opposite when it states that "one could not be certain that a chimeric TGF-β would fold correctly". And, Qian does not even mention CDMP-2. Therefore, nothing in Qian in combination with Keck suggests the specific chimeras recited in the claims of the present application or that such chimeras would properly fold and have biological activity.

Daopin teaches that TGF-β2 shares 66-80% identity with TGF-β1 through β5 and only 25-40% sequence identity with other members of the superfamily. Daopin also discloses the chimeric molecule described in Qian. As in the case of Qian, there is no teaching or suggestion in Doapin of a chimeric

molecule having a CDMP-2 finger 2 subdomain and a heel and finger 1 subdomain from a second member of the TGF-β superfamily as recited in the claims of the present application or that such a chimeric molecule would be biologically active.

Luyten discloses the sequence of CDMP-1 and CDMP-2. Luyten does not teach or suggest the presence of the finger 1, heel and finger 2 subdomains in either of the two molecules. Nor does Luyten teach or suggest any chimeric molecules as claimed in the instant application.

Griffith discloses the three dimensional structure of OP-1. Griffith also discloses the percent identity between the various members of the TGF-β superfamily. Griffith does not teach or disclose the claimed chimeric molecules wherein the finger 2 subdomain is from CDMP-2, and the finger 1 and heel subdomains are from a second member of the TGF-β superfamily.

Therefore, applicants respectfully submit that the combination of Keck, Qian, Griffith, Doapin and Luyten do not

teach or suggest the chimeric molecules as recited in the claims of the instant application.

Respectfully submitted,

James F. Haley, Jr. (Reg. No. 27,794)
Karen Mangasarian (Reg. No. 43,772)
Attorneys for Applicants
FISH & NEAVE
Customer No. 1473
1251 Avenue of the Americas
New York, New York 10020-1105
Tel.: (212) 596-9000
Fax: (212) 596-9090